The Role of Secondary Vaccine Failures in Measles Outbreaks

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Abstract: An outbreak of measles in 1985–86 in a community where measles vaccine trials had been carried out from 1974–76 allowed the assessment of the role of secondary vaccine failures in previously immunized children. A total of 188 children from the vaccine trial were followed. Of these, 175 seroconverted initially while 13 (6 per cent) required re-immunization (primary failure). A total of 13 cases of measles, eight of which were laboratory and/or physician-confirmed, were reported in this cohort. Of these, nine cases occurred in the 175 subjects who had hemagglutination inhibition test (HI) and neutralizing antibody responses following the initial immunization. These nine cases represent secondary vaccine failures. An additional four cases occurred in the 13 subjects with primary vaccine failure. We conclude that secondary vaccine failures occur and that while primary failures account for most cases, secondary vaccine failures contribute to the occurrence of measles cases in an epidemic. A booster dose of measles vaccine may be necessary to reduce susceptibility to a sufficiently low level to allow the goal of measles elimination to be achieved. (*Am J Public Health* 1989; 79:475–478.)

Introduction

Measles virus has probably infected mankind since antiquity. Only recently has the introduction of a vaccine allowed the control of measles to be considered a goal of public health.[1–3] Panum[4] showed that immunity to wild measles virus was maintained even many years after infection. However, immunity following vaccine has been more problematic, with outbreaks of measles described in immunized populations virtually since the vaccine was introduced and widely used.[5–16] In all of these reports, failure of vaccine delivery was thought to be the major factor in the outbreak rather than failure of the vaccine itself. In those cases who had been immunized and developed measles, the reason was felt to be lack of seroconversion with initial immunization, primary vaccine failure, rather than loss of protection after seroconversion had occurred, secondary vaccine failure. The attack rates in the immunized of about 5 per cent were compatible with primary vaccine failure rates. Those individuals who do not seroconvert to measles vaccine and hence are possible primary vaccine failures may be detected by serology and given further vaccine if desired. Secondary vaccine failures who have seroconverted but are not protected cannot be so identified. Gustafson[17] has recently described an outbreak in Texas in a well-immunized population where primary vaccine failure was thought to be a more important factor than vaccine delivery.

We had the opportunity to study the incidence of measles in a population of children who had participated in measles vaccine trials and who had antibody studies carried out following immunization. We report here on the relative importance of primary and secondary vaccine failures on the incidence of self-reported measles in a well-immunized population in the 10 years following immunization. As present and future control of measles is highly dependent on the induction of immunity and the maintenance of protection to prevent measles,[18] these findings may indicate the possible success or failure of measles elimination programs.

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© 1989 American Journal of Public Health 0090-0036/89$1.50

The Setting

Boundary Health Unit (BHU), a public health unit funded by the Ministry of Health of the Province of British Columbia, serves a suburban and rural community close to the major metropolitan center of Vancouver. In 1985, the year of the start of the measles outbreak, there were 271,141 residents in the 480 square kilometer area administered by the unit. Of these residents, 8.1 per cent were under age 5, 16.7 per cent were aged 5–14 years, and 31.7 per cent were aged 25–44 years. The mean family income was $29,008. The mean family size was 3.0 individuals. There are 124 public and private schools with an enrollment of 34,218 in kindergarten to grade 7, and 21,178 in grades 8–12.

Vaccine trials were carried out from January 1974 to February 1976. There were approximately 6,000 one-year-olds in 1974–75 eligible for measles immunization at one year of age. Of the number potentially eligible, 382 volunteered for the study and were enrolled. Connaught Laboratories Limited of Willowdale, Ontario conducted the measles vaccine trials to compare vaccine produced by them to vaccine from Merck, Sharp, and Dohme, Ltd. Both vaccines contained a live further attenuated measles strain and both were given as a single product. Children were immunized at approximately one year of age after an initial serum specimen was drawn. A second sample was drawn one month later. Repeat samples were done in the immunized children who could be located at three and five years. All serum samples obtained in the vaccine trial were tested for hemagglutination inhibition and for neutralizing antibodies by Connaught.

While British Columbia has experienced a decline in the numbers of measles cases reported, outbreaks have continued to take place. A measles epidemic occurred in the province from 1984 to 1986 involving 7,479 reported cases for the 12 months from September 1985 to August 1986. Of these, a total of 744 cases were reported from the BHU (354 males and 390 females); 60 (8.5 per cent) were confirmed by the Virology Section of the Provincial Laboratory, BC Ministry of Health. The peak of the epidemic occurred from the end of January 1986 to the middle of March 1986 with cases occurring until the second week of June 1986. The mean age of reported cases was 12 ± 5.6 years. The largest proportion of cases (42.7 per cent) occurred in the age group 10–14 years.

Methods

During May–June 1986, all children who had taken part in the 1974–76 vaccine trials were identified from the trial

center's records. An attempt was made to contact them at their last known address using school lists to locate additional children. The child and his/her parents were contacted to obtain consent to participate in the follow-up study. For those who consented, a blood sample was obtained from the child, and a questionnaire was administered by study personnel to the child and a parent. The questionnaire sought information about the immunization history and possible cases of measles in the child and in family members. The children in the vaccine trial who were located and enrolled in the follow-up study will be referred to as the cohort.

The measles hemagglutination (HI) antibody levels and the measles neutralization titers were both determined by methods described by Gershon and Krugman.[19] The measles IgM (immunoglobulin M) levels were determined by a method adapted by Connaught Laboratories Ltd., and are on file.

Antibody levels were analyzed using geometric mean titer (GMT) as doubling concentrations had been used for all specimens in the vaccine trial. The samples were run in different years. Although the methods for HI and NA were similar over the time period, variations in materials and instruments makes direct comparison of levels in different years inadvisable. This is particularly true of the initial and 1986 samples. We have thus looked at samples within years and did not analyze titers serially.

Primary vaccine failure is defined for this paper as failure to have neutralizing antibodies following immunization, whether the first or subsequent immunization. Secondary vaccine failure is defined as a lack of protection in an individual who had documented neutralizing antibody titer ≥ 1:4 post-immunization. Seroconversion is defined as a four-fold or greater rise in hemagglutination titer, or a detectable titer in an individual who had no previous detectable antibodies.

Results

A total of 382 infants had been enrolled in the vaccine trials. Due to an unbalanced design, 265 received vaccine produced by Connaught, while 117 received measles vaccine produced by Merck. A total of 225 of the 382 families were contacted. Thirty seven gave information but no sample was obtained. Thus for the follow-up study, a total of 188 subjects (49.2 per cent of the vaccine trial participants) were located and had data and blood samples collected (cohort), while the remaining 194 (51.8 per cent) were not located or did not enter the follow-up study (lost). Of the cohort, 129 and 59 members had received Connaught and Merck vaccines respectively, the same ratio as in the original trial. As seen in Table 1, the cohort and lost groups were similar.

The proportion of the cohort and lost groups subsequently followed in the vaccine trials was 26 per cent of the cohort group and 8 per cent of the lost group recalled at a mean of 58 months for both groups. The titers for both groups at each follow-up period were similar except for higher HI and NA titers in the cohort group at 30.4 and 31.5 months respectively. By 58 months, the antibody titers in both groups were similar.

The mean age at immunization was 1.04 years for the cohort; 23 cohort members had more than one immunization; 13 were failures in the cohort group and 12 individuals were reimmunized as part of outbreak control measures. Seroconversion rates were similar for both vaccines.

Thirteen children in the cohort group (6.9 per cent) were reported to have had measles subsequently. One of these cases was laboratory confirmed. Neutralizing antibody had been demonstrated in this individual post initial immunization. Eight cases of measles in the cohort were confirmed by a physician. Among the 13 cases of measles, five had received Merck vaccine, eight Connaught. Of these 13 cases, two had measles at age 2, four at ages 6–8 (the 1980 outbreak), and seven at ages 10–12 (the 1985–86 outbreak).

As seen in Table 2, of the 13 subjects in the cohort who did not seroconvert initially to NA, 10 underwent repeat immunization with antibody testing and all 10 seroconverted. One of these 10 was reported to have had measles. There were an additional two infants who had neither a second immunization nor subsequent antibody titers (primary vaccine failures) and both of these children were reported to subsequently have had measles. The remaining child with measles received a repeat immunization but seroconversion was not documented; the latter child was also reported to have had measles. Overall, four of 13 (31 per cent) of those who were initial vaccine failures subsequently had measles. These four cases were all physician-confirmed and three occurred in 1985–86. In those whose follow-up antibody levels were considered protective, nine of 175 (5 per cent) subsequently had measles. These nine cases were secondary vaccine failures. Four of the nine cases were physician-confirmed and four were diagnosed in the 1985–86 outbreak. The attack rates (and 95% confidence intervals) in those who converted on initial vaccination and those who did not were 31 per cent (9, 61) and 5 per cent (2, 10), respectively.

In the cohort, the initial laboratory titers differed between those with and without subsequent measles (Table 3) in that both HI and NA titers were lower in the group who subsequently developed measles. This was observed both for those who had ever had measles and for those who had measles in the 1985–86 epidemic.

The results of the samples taken in 1986 indicated that the mean HI titers in the cohort members who reported measles was higher than in those who did not (geometric mean titer 30 vs 19). This was even more pronounced if only

TABLE 1—Comparison of 188 Children Followed from Original Vaccine Trial (cohort) and 194 Children Lost to Follow-up (lost)

Parameter	Cohort (%)	Lost (%)
Number	188	194
Mean Age at Immunization	1.04 ± 0.10	1.06 ± 0.14
Seroconversion: HI	177 (94.1)	185 (95.4)
Seroconversion: NA	175 (93.1)	185 (95.4)
Total Seroconversion	185 (98.4)	193 (99.5)

TABLE 2—Reported Measles Cases in the 188 Cohort Children Stratified by NA Response to Measles Vaccine

Initial response	Total	Number Reporting Measles	Per Cent Attack Rate (95% CI)
Initial non-conversion	13	4	31
Repeat immunization with conversion	10	1	(9, 61)
No repeat immunization	2	2	
Repeat immunization/conversion unknown	1	1	
Initial seroconversion*	175	9	5
			(2, 10)

*Seroconversion defined as NA greater than 1:4

TABLE 3—Geometric Mean Titers for the 188 Cohort Children Stratified by Reporting of Subsequent Measles

Measles History	Geometric Mean Titers*		
	Initial HI	Final HI	Initial NA
Ever had measles			
yes	14.4	30.2	8.9
no	36.3	18.6	19.5
Measles in 1985–86			
yes	8.8	40.3	7.2
no	35.8	18.7	19.2

**initial* refers to the sample following immunization in the vaccine trial; *final* refers to the 1986 follow-up sample.

measles cases with dates of onset in 1985–86 were used (40 vs 19).

The measles specific IgM results were negative for all 188 members of the cohort. Specifically, none of the seven who reported measles in the 1985–86 outbreak were IgM positive. The samples for the IgM determinations were taken 13 and seven months after reported disease in two individuals, four months post infection in three subjects, two months in one, and two weeks in the other. A positive result may have been expected in five of these cases.

Discussion

Although these children were originally enrolled in a vaccine trial, their subsequent experience with measles does not appear to have been due to the differences in vaccines being tested. The control product from Merck has been widely used in Canada and the US at that time and since. Although the Connaught vaccine was not marketed, the proportion of cases who seroconverted and who subsequently developed measles was not significantly different from the Merck immunized children. The similarities in the located and not located groups within the vaccine trial population indicate that a bias in the follow-up is not likely to account for the experience of the cohort with respect to measles.

All of these children had neutralizing antibody detected postimmunization although only 95 per cent seroconverted with the first immunization as might be expected.[18,20] All of these children would conventionally be considered protected including those who required re-immunization.[21] In those in whom seroconversion had been documented, any subsequent measles must be considered a secondary vaccine failure as defined by Frank, *et al.*[22] Although documented by Cherry,[8] Frank, *et al*,[22] did not consider secondary failure a major contributor to the measles elimination program failures.

The measles experience of this cohort was considered over the life experience of the child. With the difficulty in making the clinical diagnosis of measles, this may result in the overestimation of the number of cases. Nevertheless, the reported cases in the cohort took place during reported measles outbreaks in British Columbia. During the recent outbreak there was one laboratory-confirmed and a number of physician-confirmed cases reported. Following the measles, HI antibodies demonstrated a rise over time in those reporting measles compared to those not reporting measles. All of these observations would tend to validate the cases reported. We conclude that the reported cases in the cohort represent measles in children who had seroconverted and hence are secondary vaccine failures.

Within the cohort, there were predictors of subsequent measles. Children who required re-immunization because of an initial vaccine failure were six times as likely to have measles as those who seroconverted with a single dose. Even after seroconversion, the mean titers of seroconverters who reported measles in the 1985–86 outbreak were less than those who did not report measles (HI 35.8 vs 8.8; NA 19.2 vs 7.2). These data indicate that the initial immunization response predicts subsequent risk of measles and that the risk depends on both seroconversion and on the titer of antibody produced at approximately one month following immunization. These low titers may become undetectable more quickly than higher titers although other investigators have not found that time from immunization was a factor in measles outbreaks.[6,23–25]

In our cohort, none of the five recent cases was found to be IgM positive. Nagy, *et al*,[23] found IgM responses in 77.4 per cent of those who had been vaccinated. They concluded that those who had an IgM response represented a primary vaccine failure, whereas those with HI increases or a high titer were secondary vaccine failures. Gustafson, *et al*,[17] found cases only in the group seronegative early in the epidemic, with all appropriately tested cases IgM positive. They concluded that, as no cases occurred in the seropositive group, the outbreak they investigated was due to primary vaccine failures. The situation in our outbreak was markedly different as 184 of 188 individuals in the cohort were known to be seropositive following immunization. Although it is possible that all of the cases of measles occurred in those who had lost antibody, as explained by the lower initial titers in the cases,[24,25] we could not confirm this. The lack of IgM response in our group is in contrast to the data of Gustafson[17] and Nagy,[23] although the very small numbers in our group make this lack of an IgM response imprecise. The preexisting antibody titer results on our cohort confirm that secondary vaccine failure was important in our study population.

The ultimate control of measles has been predicted with models developed by Anderson and May[26] and Levy[16]. The role of secondary vaccine failure has not been considered in these models. Neither was it considered important by Frank, *et al.*[22] We feel that the documentation of an attack rate approximating 6 per cent over the 10–12 years post-immunization in a cohort of individuals with known primary vaccine seroconversion must prompt further study into the role of secondary vaccine failure in measles outbreaks. Nkowane, *et al*,[6] found that at least 48 per cent of their cases occurred in adequately immunized individuals. Although the outbreak they investigated lasted only four generations, they concluded that vaccine failures played a role in transmission.

If a significant role is established for secondary vaccine failure, this must be taken into account in the predictions of measles control programs. The assumption that measles immunity as induced by vaccine is as high as the seroconversion rate appears to be an overestimate of the true situation. Routine booster immunization of all children rather than for select groups,[24] in order to reduce the numbers of primary vaccine failures and to boost the titers in all children, may be necessary to eliminate measles. It is clear that reliance upon measles antibody studies, even when neutralizing antibody is measured, only gives an estimate of the immune status of the individual. The clarification of the constituents of immunity to measles may allow the develop-

ment of vaccine which will more closely stimulate the same immune response that is induced by wild measles infection. Until this is done, it appears that we will continue to see measles epidemics in well-immunized populations and that these epidemics will be due to both primary and secondary vaccine failures.

ACKNOWLEDGMENTS

The authors would like to acknowledge Dr. Shirley E. Johnson, Wai Ing, and J.B. Campbell and his staff at Connaught Laboratories Limited for their assistance in the conduct of this study.

This study was supported in part by grant number 05(EF-86) from the British Columbia Health Care Research Foundation. Dr. Schechter is supported by a National Health Research Scholar Award, Health and Welfare Canada.

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